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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: USE OF REBOXETINE FOR THE TREATMENT OF HOT FLASHES

(57) Abstract: This patent application describes a method for treating or preventing hot flashes in a patient suffering therefrom comprising administering a therapeutically effective dose of a compound selected from reboxetine, S,S-reboxetine or pharmaceutically acceptable salts thereof, to the patient.

USE OF REBOXETINE FOR THE TREATMENT OF HOT FLASHES

Field of the Invention

This invention describes a new treatment for hot flashes. The treatment involves the administration of the drug reboxetine, pharmaceutically acceptable salts thereof, derivatives thereof, or prodrugs thereof to a patient in need thereof.

Background of the Invention

Hot flashes are a common complaint. The patient experiences a sudden onset of heat, which generally starts in the face and then can progress to the neck, chest and the rest of the body. Often the attacks are accompanied by a red flush of the skin and/or profuse sweating. These attacks, which can occur several times a day, can be exceedingly uncomfortable to the person experiencing them.

Although the exact cause of hot flashes is not known, they are often attributed to an imbalance of the patient's hormone system. A large group of patients, who experience hot flashes, are menopausal women. To date, this group of patients has often received estrogens or hormone replacement therapy to alleviate or prevent menopause symptoms, including hot flashes (E. Daly et al., Br. Med. J. 1993; 307:836–840). However, some women are reluctant to agree to a hormone therapy. A range of "natural" therapies on a herbal basis including black cohosh, phytoestrogens, flax seed, red clover, vitamin E (D.L. Barton et al., J. Clin. Oncol. 1998, 16:495–500), ginseng and evening primrose oil have been advocated as possible medications (University of Wisconsin Medical School, online courses, "Alternatives for Menopausal Symptoms: A Review of the Evidence"; www.cme.wisc.edu/online/menopause). However, not all of these therapies are effective (K.I. Pritchard, The Oncologist, 2001, 6(4), 353-362).

Other medications, which have been suggested, are selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine hydrochloride (Prozac; C. Loprinzi; www.medicine-news.com/articles/pharma/misc/hotflashes.html) and paroxetine hydrochloride (Paxil; V. Stearns et al., Ann. Oncol., 2000, 11: 17-22) as well as

venlafaxine hydrochloride (Effexor; C.L. Loprinzi et al., J. Clin. Oncol., 1998, 16: 2377-2381), which is a serotonin and norepinephrine reuptake inhibitor.

Low doses of megestrol acetate have also been shown to reduce the frequency of hot flashes in both men and women (Loprinzi et al., N. Engl. J. Med. 1994, 331:347–351). Chronic adrenal insufficiency and weight gain can be side effects. Transdermal clonidine has also been employed to reduce the frequency and severity of hot flashes (R.M. Goldberg et al., J. Clin. Onc. 1994, 12:155–158); R.M. Goldberg et al., J. Clin. Oncol. 1994, 12:155–158; L.R. Laufer, Obstet. Gynecol. 1982, 60:583–586). However, side effects such as drowsiness, fatigue, and symptoms of low blood pressure in some patients were observed.

Both men and women can suffer from hot flashes as a side effect of cancer therapy. Certain drugs such as Tamoxifen (Nolvadex), which is used to treat breast cancer, as well as Lupron (Leuprolide) and Zoladex (Goserelin), which are employed in the therapy of prostate cancer, can lead to heat sensations. Bilateral orchiectomy for prostate cancer or testicular cancer also affects the hormone system so that patients can subsequently suffer from hot flashes. Especially in the case of cancer patients, hormone replacement therapy is often not advised, because there is a concern that cancer regrowth can be stimulated.

In view of the disadvantages of the prior art, there remains a need for further medications, which can reduce the number and/or severity of hot flashes. It has now been found that reboxetine is effective in treating these attacks.

Summary of the Invention

The present invention provides a method of treating and/or preventing hot flashes in a patient suffering therefrom comprising administering a therapeutically effective dose of a compound selected from reboxetine, pharmaceutically acceptable salts thereof, derivatives thereof, or prodrugs thereof to the patient.

In a further embodiment the use of a compound selected from reboxetine, pharmaceutically acceptable salts thereof, derivatives thereof, or prodrugs thereof for the manufacture of a medicament to treat and/or prevent hot flashes is disclosed.

The present invention also refers to a method of treating and/or preventing a symptom of hormonal variation in a patient suffering therefrom comprising administering a therapeutically effective dose of a compound selected from reboxetine, an enantiomer or diasteromer, a pharmaceutically acceptable salt thereof, a derivative thereof, or a prodrug thereof to the patient.

Detailed Description of the Invention

Reboxetine is the generic name of the pharmaceutical substance with the chemical name of 2-[α-(2-ethoxy)phenoxybenzyl]morpholine, and its pharmaceutically acceptable salts. Reboxetine is also known under the trade names of VESTRA, EDRONAX, PROLIFT, INTEGREX, and NOREBOX. Besides the racemic mixture of R,R- and S,S-enantiomers, preferably the pure S,S-enantiomer can be employed in the present invention.

Reboxetine acts as an antidepressant. Antidepressants are frequently grouped into categories or "generations". The first generation of antidepressants were usually tricyclic antidepressants such as maprotiline that affected various neurotransmitter systems and are associated with many undesirable side effects. The second generation of antidepressants, such as mianserine, mirtrazapine and trazodone are largely devoid of anticholinergic action and their adrenolytic and antihistaminic effects are weaker. These are contrasted with the third generation of antidepressants (e.g. SSRI, ipsapirone, viloxazine, reboxetine, bupropione) that mediate only one of the three main neurotransmitter systems for depression (5-HT, noradrenaline, dopamine) and they do not affect muscarine, histamine and adrenergic cerebral systems. J. Svestka. "Antidepressives of the 3rd, 4th and 5th generation", Cesk-Psychiatr. 1994 Feb; 90(1):3-19 (Czech).

Reboxetine, however, does not act like most antidepressants. Unlike tricyclic antidepressants and even selective serotonin reuptake inhibitors (SSRIs), reboxetine is ineffective in the 8-OH-DPAT hypothermia test, indicating that reboxetine is not a selective serotonin reuptake inhibitor but rather that it is selective for the noradrenergic system. Thus, reboxetine is not an SSRI, rather it is considered a novel, selective, noradrenaline-reuptake inhibitor (NARI). B.E. Leonard, "Noradrenaline in basic models of depression". European-Neuropsychopharmacol. 1997 Apr; 7 Suppl 1: S11-

6; discussion S71-3. Unlike most drugs, reboxetine is a highly selective norepinephrine uptake inhibitor, with only marginal serotonin and no dopamine uptake inhibitory activity. The compound displays only weak or no anti-cholinergic activity in different animal models and is devoid of monoamine oxidase (MAO) inhibitory activity.

Reboxetine is highly potent and fast acting. Our investigations indicate that reboxetine has potent antireserpine activity and combines the inhibitory properties of classical tricyclic antidepressants on the reuptake of noradrenaline with an ability to desensitize J-adrenergic receptor function without showing any appreciable interaction with muscarinic cholinergic and I-adrenerigic receptors. Moreover, reboxetine shows less vagolytic activity than other tricyclic antidepressants.

The inventors have discovered that, because of its unique properties, reboxetine is particularly useful for treating or preventing hot flashes. Furthermore, the inventors have discovered that reboxetine can be used to treat or prevent symptoms of hormone variation in a patient.

In the present invention reboxetine can be employed in its free base form. Furthermore, reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance can be used such as the succinate or fumarate salt thereof. The use of pharmaceutically acceptable derivatives as well as of prodrugs of reboxetine is also possible. The expression "prodrug" denotes a derivative of a known direct acting drug, which derivative has enhanced delivery characteristics and therapeutic value as compared to the drug, and is transformed into the active drug by an enzymatic process, for example by hydrolysis in blood, or a chemical process [see H. Bundgaard, "Design of Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities", in Design of Prodrugs (H. Bundgaard, ed.), Elsevier, N.Y. (1985)].

Reboxetine and its various derivatives and a method of synthesis therefore are described in U.S. 4,229,449 (Melloni et. al.), which is incorporated herein by reference. Methods of preparing reboxetine are also described in US 5,068,433 (Melloni et. al.) and in US 5,391,735 (Melloni et. al.), both of which are incorporated by reference.

Reboxetine is useful in treating or preventing hot flashes by reducing the number and/or severity of the attacks. The hot flashes treated according to the invention can be due to a number of causes. Reboxetine can be employed to treat or prevent hot flashes, which occur as a symptom of the postmenopause phase, but it is also effective if the hot flashes have other causes. In particular, various medical therapies can imbalance the hormone system of both female and male patients resulting in attacks of hot flashes.

Female patients having a low level of estrogen are prone to suffer from hot flashes. This deficiency can be due to radiation therapy, which can prematurely induce the menopause, or can be caused by specific medications such as anti-estrogen treatment or certain drugs (e.g. Tamoxifen (Nolvadex)).

Androgen deprivation can be a cause of hot flashes in men. Again the imbalance of the hormone system can be drug-induced (e.g. Lupron (Leuprolide) and Zoladex (Goserelin)) or be radiation-induced. Surgery such as bilateral orchiectomy for prostate cancer or testicular cancer is a further possible cause.

Reboxetine can be administered to the patient in the form of a pharmaceutical composition. Pharmaceutical compositions and methods of administration, which are useful in the present invention, are described, for example, in US 4,229,449 at col. 18, lines 33-66. This reference is specifically incorporated herein by reference. Pharmaceutically acceptable carriers and excipients as well as other adjuvants are known in the art and can be selected based on the desired route of administration.

Reboxetine can be administered in a dose range of active ingredient from about 1 to over 20 mg/kg. It is more commonly provided in dosages of from 1 to 20 mg per patient per day. The compound may be administered by any suitable method including a convenient oral dosage form. A preferred method is oral dosing twice a day. The preferred dose range is 4 to 10 mg per patient per day and the most preferred dose is 6 to 8 mg or 8 to 10 mg per patient daily, depending upon the patient, delivered twice a day (b.i.d.). It can also be given at dosages of 2, 4, 6, 8, 10 or 12 mg per patient per day or fractions thereof. For example, suitable administrations could be 4 mg in the morning and 2 or 4 mg in the evening or 6 mg in the morning and 4 mg in the evening. In some patients the ideal dosing would be 3-5 mg in the morning and 3-5 mg in the evening. A skilled practitioner would be expected to determine the precise level of

dosing. The ideal dosing would be routinely determined by an evaluation of clinical trials and the needs of the patient.

Reboxetine is effective in treating hot flashes. It is especially useful for treating patients who are suffering from or who have suffered from cancer and consequently should not receive hormone replacement therapy. The present invention now provides a novel and safe method of treating these undesirable attacks.

Claims

1. A method for treating or preventing hot flashes in a patient in need thereof comprising administering a therapeutically effective dose of a compound selected from reboxetine or S,S-reboxetine, a pharmaceutically acceptable salt thereof, a derivative thereof, or a prodrug thereof to the patient.

2. A method of claim 1, wherein the patient is female.

3. A method according to claim 2, wherein the hot flashes are menopause or postmenopause symptons.

4. A method according to claim 2, wherein the hot flashes are due to medical treatment.

5. A method according to claim 2, wherein the hot flashes are caused by radiation therapy.

6. A method according to claim 2, wherein the hot flashes are drug-induced.

7. A method according to claim 2, wherein the patient is receiving anti-estrogen therapy.

8. A method according to claim 2, wherein the patient is suffering from or has suffered from cancer.

9. A method according to claim 5, wherein the cancer is breast cancer.

10. A method according to claim 1, wherein the patient is male.

11. A method according to claim 10, wherein the hot flashes are caused by radiation therapy.

12. A method according to claim 10, wherein the hot flashes are drug-induced.

13. A method according to claim 10, wherein the patient has androgen deprivation.

14. A method according to claim 10, wherein the patient is suffering from or has suffered from cancer.

15. A method according to claim 14, wherein the cancer is prostate cancer or testicular cancer.

16. The method according to claim 1, wherein the reboxetine dose range is 4 to 10 mg per patient per day.

17. The method according to claim 1, wherein the reboxetine dose range is 6 to 8 mg per patient per day.

18. The method according to claim 1, wherein the compound is administered in the form of a pharmaceutical composition additionally comprising a pharmaceutically acceptable carrier or excipient.

19. The use of a compound selected from reboxetine, or S,S,-reboxetine, or a pharmaceutically acceptable salts thereof, a derivative thereof, or a prodrug thereof for the manufacture of a medicament to treat or prevent hot flashes.

20. The use according to claim 19, wherein the reboxetine dose range is 4 to 10 mg per patient per day.

21. The use according to claim 19, wherein the reboxetine dose range is 6 to 8 mg per patient per day.

22. A method for treating or preventing symptoms of hormonal variation in a patient suffering therefrom comprising administering a therapeutically effective dose of a compound selected from reboxetine, a pharmaceutically acceptable salt thereof, a derivative thereof, or a prodrug thereof to the patient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/22491

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5375 A61K45/06 A61P5/24 A61P15/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, SCISEARCH, CANCERLIT, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 01973 A (MARSHALL ROBERT CLYDE ;UPJOHN CO (US); WONG ERIK H F (US); BIRGERS) 11 January 2001 (2001-01-11)	22
Y	page 1, line 3 - line 9 page 2, line 11 - line 13 page 3, line 29 -page 6, line 14 page 8, line 1 - line 10 page 9, line 10 - line 17 page 10, line 3 - line 28 page 11, line 28 -page 12, line 13 page 13, line 19 -page 14, line 2 page 19, line 20 - line 27 page 25, line 14 - line 22 page 27, line 3 - line 25 page 28, line 15 - line 23 claims 1,18,23,38,41,52	1-3, 16-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2003	13/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, E

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 753 651 A (DEPADOVA ANTHONY S) 19 May 1998 (1998-05-19) column 7, line 1 - line 11	1-3, 16-21
Y	WO 02 40006 A (LILLY CO ELI ;MICHELSON DAVID (US); THOMASSON HOLLY READ (US)) 23 May 2002 (2002-05-23) page 1, line 6 - line 11 page 2, line 12 - line 15 page 5, line 1 - line 20 page 7, line 11 - line 13 page 13, line 1 - line 7 page 15, line 7 - line 17	1,16-21
Y	US 6 358 944 B1 (LEDERMAN SETH ET AL) 19 March 2002 (2002-03-19) column 5, line 12 - line 18	1,16-21
A	LOPRINZI C L ET AL: "Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial." LANCET. ENGLAND 16 DEC 2000, vol. 356, no. 9247, 16 December 2000 (2000-12-16), pages 2059-2063, XP004264310 ISSN: 0140-6736 abstract page 2062, column 1, paragraph 6 -column 2, paragraph 1 page 2063, column 1, paragraph 1	1-21
A	SWINT S.: "Prozac shows promise for hot flashes in breast cancer survivors" MEDICINE NEWS, 'Online! 1999, pages 1-4, XP002265194 Retrieved from the Internet: <URL:www.medicine-news.com/articles/pharma/misc/hotflashes.html> 'retrieved on 2003-12-08! cited in the application the whole document	1-22
A	FREEDMAN ROBERT R ET AL: "Clonidine raises the sweating threshold in symptomatic but not in asymptomatic postmenopausal women" FERTILITY AND STERILITY, vol. 74, no. 1, July 2000 (2000-07), pages 20-23, XP001176742 ISSN: 0015-0282 abstract page 23, column 1, paragraph 2 - paragraph 3 page 23, column 2, paragraph 1	1-22

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FREEDMAN ROBERT R: "Biochemical, metabolic, and vascular mechanisms in menopausal hot flashes" FERTILITY AND STERILITY, vol. 70, no. 2, August 1998 (1998-08), pages 332-337, XP001176734 ISSN: 0015-0282 abstract page 332, column 2, paragraph 2 page 336, column 1, paragraph 4 page 336, column 2, paragraph 2 ---	1-22
A	RADLMAIER A ET AL: "HOT FLUSHES MECHANISM AND PREVENTION" MURPHY, G. P. AND S. KHOURY (ED.). PROGRESS IN CLINICAL AND BIOLOGICAL, 1989, pages 89-90, XP008025613 INTERNATIONAL SYMPOSIUM, PARIS, FRANCE, JUNE 29-JULY 1, 1988. XXX+913P. ALAN R. LISS, INC.: NEW YORK, NEW YORK, USA. ILLUS 1989 Series: Progress in Clinical and Biological Research (ISSN 0361-7742) ISBN: 0-8451-5153-3 the whole document ---	1-22
A	HOLM K J ET AL: "Reboxetine: A review of its use in depression" CNS DRUGS 1999 NEW ZEALAND, vol. 12, no. 1, 1999, pages 65-83, XP002936123 ISSN: 1172-7047 abstract page 68, paragraph 5 - paragraph 6 figure 5 page 80, column 1, paragraph 1 page 81, column 2, paragraph 3 ---	1-22
P,X	WO 03 049724 A (YANG CHARLES RENKIN ;LILLY CO ELI (US); BYMASTER FRANKLIN PORTER () 19 June 2003 (2003-06-19) page 2, line 27 -page 3, line 2 page 5, line 9 - line 30 page 20, line 10 - line 11 ---	22
P,X	WO 03 039598 A (CYPRESS BIOSCIENCE INC) 15 May 2003 (2003-05-15) page 24, line 6 - line 14 page 37, line 28 -page 38, line 10 ---	22
P,A	WO 03 000699 A (ENGLBERGER WERNER GUENTER ;GERMANN TIENO (DE); HAURAND MICHAEL (DE) 3 January 2003 (2003-01-03) page 41, line 21 -page 42, line 13 ---	1-22

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 03/22491

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 078691 A (LILLY CO ELI ;GARNETT TIMOTHY JOHN (US); WALLACE OWEN BRENDAN (US)) 10 October 2002 (2002-10-10) page 2, line 16 -page 3, line 8 page 3, line 30 -page 4, line 3 page 5, line 10 - line 13 page 8, line 31 -page 9, line 16 claim 1 -----	1-22

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/22491

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-18 and 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-22 relate to compounds which actually are not well-defined. The use of the definitions "a derivative thereof" and "a prodrug thereof" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds which are well-defined in the claims and the description, namely (racemic) reboxetine, S,S-reboxetine, or pharmaceutically acceptable salts thereof. Moreover, present claim 22 relates to a disease which actually is not well-defined. The use of the definition "symptoms of hormonal variation" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the real and defined disease mentioned in claims 1-21, namely hot flashes, with due regard to the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0101973 A	11-01-2001	AU 5633700 A	22-01-2001
		BR 0012136 A	11-06-2002
		CA 2375908 A1	11-01-2001
		CN 1379672 T	13-11-2002
		CZ 20014625 A3	14-08-2002
		EP 1196172 A2	17-04-2002
		HU 0201623 A2	28-09-2002
		JP 2003503450 T	28-01-2003
		NO 20016406 A	19-02-2002
		SK 19382001 A3	02-07-2002
		WO 0101973 A2	11-01-2001
		US 2002061910 A1	23-05-2002
		US 2002086864 A1	04-07-2002
		US 2002107249 A1	08-08-2002
		US 2002128173 A1	12-09-2002
		US 2003040464 A1	27-02-2003
		US 6465458 B1	15-10-2002
		ZA 200110325 A	14-03-2003
US 5753651 A	19-05-1998	US 5464854 A	07-11-1995
		AU 2429895 A	29-11-1995
		CA 2189143 A1	09-11-1995
		EP 0759754 A1	05-03-1997
		WO 9529674 A1	09-11-1995
WO 0240006 A	23-05-2002	AU 1775702 A	27-05-2002
		CA 2426069 A1	23-05-2002
		CZ 20031339 A3	15-10-2003
		HR 20030384 A1	31-08-2003
		HU 0301863 A2	29-09-2003
		NO 20032156 A	13-05-2003
		WO 0240006 A2	23-05-2002
US 6358944 B1	19-03-2002	AU 6634000 A	13-03-2001
		AU 6635400 A	13-03-2001
		BR 0013017 A	16-04-2002
		BR 0013122 A	30-04-2002
		CA 2380373 A1	22-02-2001
		CA 2380432 A1	22-02-2001
		EP 1202721 A1	08-05-2002
		EP 1202722 A1	08-05-2002
		ES 2192156 A1	16-09-2003
		GB 2368522 A	08-05-2002
		GB 2368283 A	01-05-2002
		JP 2003506483 T	18-02-2003
		JP 2003506484 T	18-02-2003
		WO 0112174 A1	22-02-2001
		WO 0112175 A1	22-02-2001
		US 6395788 B1	28-05-2002
		US 2001046988 A1	29-11-2001
WO 03049724 A	19-06-2003	WO 03049724 A1	19-06-2003
WO 03039598 A	15-05-2003	US 2003139476 A1	24-07-2003
		WO 03039598 A1	15-05-2003
		US 2003130353 A1	10-07-2003
WO 03000699 A	03-01-2003	DE 10130020 A1	04-12-2003

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/22491

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03000699 A		WO 03000699 A1	03-01-2003
WO 02078691 A	10-10-2002	CA 2442410 A1 WO 02078691 A1	10-10-2002 10-10-2002